Case Report

Indian Journal of Cancer Education and Research
Volume 4 Number 1, January - June 2016
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.4116.4

Multiple Radiation Induced Late Changes Seen in Pelvis in a Single Patient

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Abstract

Background: Radiation sequelae can be early or late depending on the duration of occurrence. Early reactions are temporary but late reactions tend to be permanent and occur many years after treatment. Late reactions can be seen in skin, subcutaneous tissue, muscle and bone in the irradiated area. *Material & Method:* We present here a report in which we saw all the late reactions in a single patient 18 years after radiotherapy to pelvis for cancer cervix. *Results:* Our patient has bone fracture, new bone formation, bone marrow widening, muscle hypertrophy, subcutaneous fibrosis and angiokeratoma developed simultaneously after 18 years of radiotherapy to pelvic area. *Conclusion:* All these types of late toxicities are rarely seen in the same patient and we could not find any such reports in the literature.

Keywords: Late Radiation Toxicity; Bone; Muscle and Skin Simultaneously; Pelvis.

Introduction

Radiation toxicity can be divided into early and late. Nausea, skin reactions, diarrhea and neutropenia are early temporary effects whereas late effects are connective tissue fibrosis, bone fractures, skin lesions and secondary malignancy which occurs months or years after Radiotherapy. The etiology for long-term sequelae is complex and involves a cascade of cellular, vascular, and cytokine changes induced by radiation. The organs at risk during pelvic radiotherapy are colon, small bowel, bladder, ureters, urethra, genital organs, spinal cord, skin, soft tissue, muscles, bones, vasculature, nerves and lymphatic system.

One or more late radiation toxicity can be seen in survivors. Here we present a case where late reactions were seen in all tissues 18 years after radiotherapy to pelvis. The patient has bone fractures, new bone formation, widening of joint space with fluid, fatty marrow, muscle hypertrophy, subcutaneous fibrosis and angiokeratoma developing simultaneously. All these late radiation toxicities are rarely seen in same patient. We could not find any similar case reported in the literature.

Material and Methods

A 49 years female presented with burning micturation, fever, inability to walk and multiple skin lesions over pelvic area which were not responding to symptomatic treatment.

In past she had squamous cell carcinoma cervix and received external beam radiotherapy(EBRT) 50Gy/25 fractions with anterior and posterior portals delivered on alternate days on telecobalt unit followed by single fraction of Intracavitary brachytherapy 25Gy at point A on LDR unit till October 1994. Since then patient was on regular follow up and is loco regionally controlled.

In May 2011 she started pain in pelvic area with difficulty in walking. Pelvis X-ray revealed pathological fracture at right superior ischeo-pubic ramus and new bone formation in inferior ischeo-pubic rami [Figure 1]. In June 2011 patient developed multiple red, firm warty lesions over vulvar and pubic area [Figure 2] with episodes of leucorrhoea. Patient was locoregionally controlled. In September 2012 she developed low back pain and progressive difficulty in walking. Her MRI pelvis showed diffuse hyperintense signals in sacral ala and left iliac bone

with widening of left sacro-iliac joint space and enlargement of psoas muscle along with increased signals in ipsilateral iliacus piriformis and proximal adductor muscles. A loculated cyst was also seen in left iliacus muscle. Fatty marrow changes were evident in all pelvic bones [Figure 3A-B] . There was no evidence of disease at primary site except for vaginal wall thickening, extensive subcutaneous fibrosis in pelvic region and lower abdominal muscles and multiple vulvar lesions A whole body PET Scan was done which showed increased uptake (SUV 8.4) in sclerotic lesions of left sacro-iliac joints with increased joint space suggesting inflammatory sacro-ilietis. FDG non avid cortical break were seen in anterior pillar of right acetebulum, inferior pubic ramus and sacral ala indicating pathological fracture. Soft tissue hypertrophy was seen in left psoas, iliacus and piriform muscles without uptake. No uptake was seen in the vulvar lesions.

Biopsy done from one warty lesion over pubis showed hyperplastic epidermis with focal hyperkeratosis and Papillary dermis showing numerous dilated vascular spaces forming angiomatous mass confirming radiation induced angiokeratoma [Figure 4A-B]. On followup last month she had increased pain in pelvis, inability to walk, increased number of vulvar lesions and bilateral lower limb oedema.

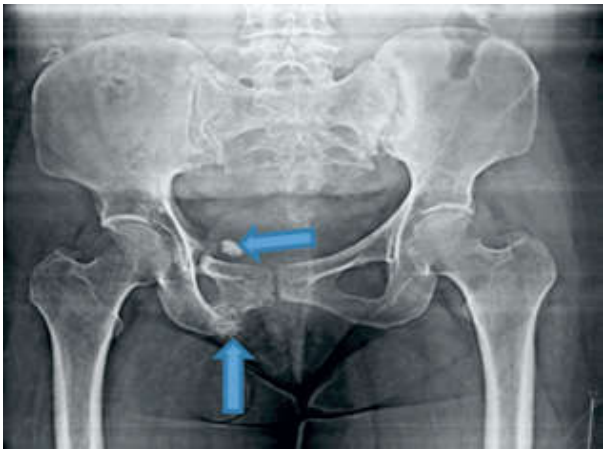

Fig. 1: Pathological fracture and new bone formation

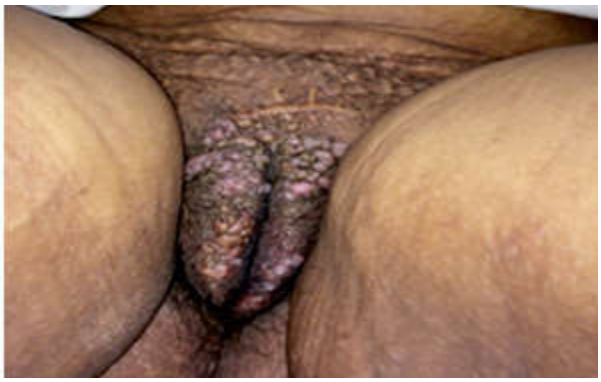

Fig. 2: Subcutaneous fibrosis and multiple nodules over vulva

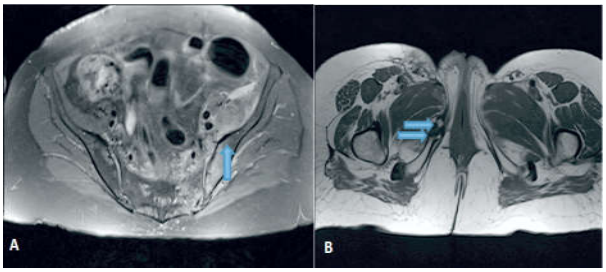

Fig. 3a & b: MRI showing fatty marrow, diffuse hyperintense signals in sacral ala and left iliac bone with widening of left sacro-iliac joint and muscle changes

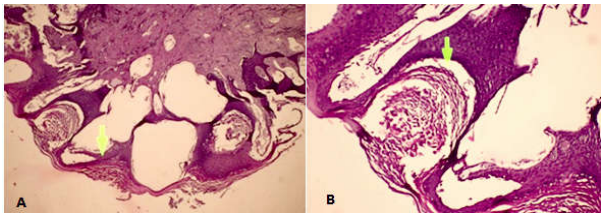

Fig. 4a & b: Showed hyperplastic epidermis with focal hyperkeratosis and Papillary dermis showing numerous dilated vascular spaces forming angiomatous

Discussion

Radiation therapy is remains to be mainstay of treatment in various malignant conditions.The frequency of radiation induced adverse effect have decreased significantly with the advent of newer technologies of radiation delivery which allows more conformity of the target tissue and homogenous dose distribution and also because of increased knowledge of tissue response to radiation.

Effects of radiation on living tissue can be divided into early and late effects, which show huge variation in terms of different patterns of response to fractionations and dose-response relations. Acute damage may be completely reversible and is rapidly repaired by rapid proliferation of stem cells [1]. Only after a delay of months or years late effects appear and these can be seen predominantly in slowly proliferating tissues, such as lung, kidney, heart, liver and central nervous system. Late damage may improve but it is never completely repaired and these late changes might result from a combination of vascular damage and loss of parenchymal cells [1].

Musculoskeletal Complication of radiotherapy are often discovered incidentally when radiographic investigations are ordered to check presence of recurrence or metastatic disease .Radiation Doses which are used routinely for treatment for Cervical cancer(CaCx) or carcinoma prostate doesn't result in acute injury to bone. Therefore late radiation induced changes in bones are characteristic and a long latent period is usually present before these changes are

detected because of slow metabolic turnover of bones [2]. These late effects include damage to osteoblasts, decreased matrix formation and osteopenia along with osteoradionecrosis, pathologic fractures and radiation induced neoplasms which are usually seen years after radiation [2]. The threshold of radiation-induced changes in the bone is thought to be 3,000cGy, with death of cells usually occurring at 5,000cGy [3,4].

Repair of damaged bone takes place with deposition of bone on unresorbed trabeculae which can be seen as focal areas of increased opacity in close proximity to areas of mottled bone with osteopenia on radiographs and patient can be initially asymptomatic but ultimately symptoms appear due to osteonecrosis or stress insufficiency fractures [5]. These changes can be attributed to the decrease in bone blood flow. This reduction in bone vascularity combined with impaired bone formation from irradiated osteoblasts result in decrease in bone density and thus resulting in fracture .Radiation can lead to obliteration endartitis and endothelial cell cytoplasmic vacuolization [6] which in turn leads to luminal narrowing in the harvesian system resulting in decreased blood flow. Also the fact that osteoblast proliferation is affected by radiation resulting in decreased bone matrix formation and bone atrophy. Thus as a end result of radiation injury osteoclast bone resorption can continue without concomitant bone formation resulting in decrease in bone density and thus fractures [7,8]. Risk factors for radiation induced pathologic factors of bones include total radiation dose, dose given per fraction, area of bone receiving radiation, size of radiation portals periosteal stripping of bone, female gender, older age, postmenopausal women, osteoporosis, and use of chemotherapy [9,10,11].

The bony structures of pelvis are frequently included in radiation portals while treating CaCx or other gynecological malignancy. Radiation induced changes in pelvis usually includes osteopenia, increased bone density and widening and irregularity of the sacroiliac joints and pelvic insufficiency fractures (PIF).These can be detected on radiographic imaging and it is important to differentiate these radiation induced changes from metastatic disease. On routine X-rays typical pattern of osteopenia is seen along with patchy areas of sclerosis and increased bone densities [12]. Sacroiliac joints may also appear widened and irregular with sclerosis [4]. Pelvic insufficiency fractures (PIF) are common in patients who have received prior radiation to pelvis.PIF usually occurs near the areas of radiation osteitis® and in close proximity of to the weight bearing joints especially adjacent to sacroiliac joints. CT scans or MRI pelvis has higher sensitivity for detection of PIF's [13,14,15,16]. The 5-year incidence of PIF in patients who have been previously irradiated patients is found to be 2.1%-13% [15,16,17]. Usually patients having PIF are asymptomatic but these may present with new onset of pain. These painful lesions may persist for months to years in symptomatic patients. Risk factors for PIF include Dose >50Gy, osteopenia, corticosteroid use and older age[16,18,19]. Clinical Presentation of our patient along with changes seen on X-rays and MRI, and presence of risk factors for PIF favors our diagnosis of radiation induced late changes.

EBRT delivered by conventional fractionation cause no damage or very little damage to mature muscle fibers [20,21]. Dose fractionation schedule is an important determinant of muscle injury. Karasec et.al [22] noted that most important determinant of delayed late muscle morbidity in patient of soft tissue sarcoma after radiotherapy is the volume of tissue receiving more than 55Gy. Withers et al [21] performed a retrospective analysis on 676 patients treated with EBRT for carcinoma tonsil and reported that 66% of late muscle complications appeared in the first 4 years after treatment injury and concluded that larger total dose and larger dose per fraction were main factors defining the rate of complication whereas overall treatment time was not. Phillips et al [23] studied human muscle response after irradiation, and observed muscle degeneration and vacuolization associated with a loss of capillaries two to four months after doses of 20Gy.

Muscle changes in response to radiation can be impressive and acute changes on MRI can be seen by bright T2 weighted signal intensity in the treated field indicating inflammation and/or edema [24]. Chronic or late changes usually seen as discrete areas of fibrosis and muscle atrophy often with overlying volume deficits corresponding to the radiation treatment portals. Lefaix et.al. demonstrated that muscle fibrosis is a common and late side effect of radiation on skeletal muscle [25]. Fibrosis is usually irreversible and results in chronic pain deformity and impaired mobility in severe cases. Delayed necrosis of striated muscle can also be seen after receiving therapeutic doses of radiation because of damage to capillaries and connective tissue. Several reports [26] also described patients of hodkins lymphoma having myopathy within the radiated muscles.

Most common histopathological changes due to post radiation myopathy are presence of nemalin rods. Other changes include variation in muscle fibre size,disorganized architecture nuclear variations and infiltration by adipocytes [27]. Pathophysiology underlying these muscle changes is due to damage to vessel and blood capillaries and their consequent

ischemia along with the inflammation. The endothelial cell are most sensitive to radiation and they exhibits swelling and necrosis acutely followed by intimal proliferation and increase in collagen content and its deposition which along with ischemia and inflammation leads to development of muscle fibrosis and which in turn causes a non specific repair reaction which causes alteration in muscle parenchyma [28,29]. Although rare, progressive muscle damage can continue for up to 10 years following treatment [29]. Radiation also affects muscle satellite cells by impairing their activation, proliferation and differentiation by preventing their mitosis by causing breaks in DNA strands which leads to inhibition of regeneration and muscle hypertrophy [30].

Changes seen in our patient can be explained by the fact that relatively large daily fractionated doses were administered to the pelvic muscles. Also the decision to use two field technique the pelvic muscle might have received larger dose pre fraction and cumulative dose than if 3 or4 field techniques have been used.

Skin reaction to radiation can be classified as early (before6 months) or late (>6 months). Early reactions include transient erythema causing vasodilatation, increased vascular permeability and edema, Epilation and skin dryness is also seen due to damage to hairfollicles and sebaceous glands, these changes are followed by dry desquamation, pruritis, scaling, hyperpigmentation and moist desquamation usually seen after 2-3weeks of radiotherapy. Late reactions include Hyperpigmentation and /or hypopigmentation, epidermal and/or dermal atrophy, skin dryness, loss of sweat glands and duct, alopecia, telactangesia, nuclear atypia nuclear atypia of basal keratinocytes and melanocytes, dyskeratosis, loss of rete ridges, disappearance of the epidermal basement membrane, fibrin formation along the dermoepidermal junction, and decreased numbers of upper dermal blood capillaries [31-34]. Hyperplasia of epidermis/ Dermis, Hyperkeratosis, Fibrosis, luminal narrowing or obliteration of vessels, radiation induced neoplasm. Radiation induced angiokeratoma is a rare phenomenon to occur and a recognized complication, [34-37]. Angiokeratomas are benign lesions thought to be telangectasias with secondary epithelial proliferation. Histologically angiokeratomas are characterised by ectatic capillaries at the dermoepidermal junction, with reactive hyperkeratosis, acanthosis, and focal papillomatosis of the overlying epidermis [39] Proposed mechanisms responsible for the development of angiokeratomas include primary degeneration of the vascular elastic tissue, increased venous pressure with consequent destruction of elastic fibers resulting in over distension, and chronic inflammation causing phlebectasia [35]. Radiation induced damage to blood vessels along with decreased blood return due to larger field sized used in treatment could lead to increase in venous blood pressure which in turn is known to cause angiokeratoma. A possible mechanism is vascular injury because of radiotherapy-induced free radical production. Blood vessels are relatively resistant to radiation hence this toxicity is very rare to *occur.* Patients having angiokeratomas are mostly asymptomatic but sometimes patient may present with complains of dyspareunia, bleeding or pus discharge from some of the lesions and these increase in number and size slowly in radiated area. Therapy is sometimes required when there is continuous bleeding, progressive pain or anxiety [35]. In symptomatic cases therapy is indicated and treatment modalities include surgical excision, electrocauterization, cryotherapy or laser treatment, the choice of which largely depends on size of the lesion [38].

Our patient also showed vulvar lesions gradually increasing in number and size with discharge but no bleeding resulting in dyspareunia and psychological burden to patient and was offered treatment in form of surgery but patient refused surgery hence a decision to treat conservatively was taken.

Presence of late toxicities involving bones, muscle and skin lesion in form of vulvar angiokeratoma in a single patient is very rare and we could not find any such case in literature.

The most likely cause for the development of these late effects in the present case was the schedule and technique used for the delivery of radiation in an overweight patient with antero-posterior separation of 26cm leading to increased Integral dose .

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